

REMARKS

In the Office Action dated April 25, 2003, claims 1-56 were examined with the result that all claims were rejected. The Examiner made the rejection final. In response, Applicant submits the following remarks. In view of these remarks, reconsideration of this application is requested.

In paragraphs 2 and 3 of the Office Action, the Examiner rejected claims 1-56 under the doctrine of obviousness type double patenting. However, before dealing with the double patenting rejections, Applicant would like to turn to paragraphs 4 and 5 of the Office Action where the Examiner rejected the claims under 35 USC §103(a). Applicant will return to the double patenting rejections after discussing the obviousness rejections.

In the Office Action, the Examiner rejected claims 1-4 and 9-32 under 35 USC §103(a) as being unpatentable over DeLuca et al U.S. Patent 5,945,410. The Examiner states that the DeLuca et al '410 patent teaches a generic group of 2-alkyl-19-nor-vitamin D compounds and exemplifies in particular 2-methyl-19-nor-1 α ,25-dihydroxyvitamin D₃. Thus, since the compounds disclosed in the '410 reference are adjacent lower homologs of the instantly claimed compounds, the Examiner concludes that this close structural similarity renders the instantly claimed 2-ethyl compounds obvious.

Also in the Office Action, claims 5-8 and 33-56 were rejected under 35 USC §103(a) as being unpatentable over DeLuca et al U.S. Patent 5,843,928. The Examiner states that the DeLuca et al '928 reference teaches a generic group of 2-alkylidene-19-nor-vitamin D compounds and exemplifies in particular 2-methylene-19-nor-1 α ,25-dihydroxyvitamin D₃. Accordingly, since the compounds disclosed in the '928 reference are adjacent lower homologs of the instantly claimed compounds, the Examiner concludes that this close structural similarity renders the instantly claimed 2-ethylidene compounds obvious.

In response to the above rejections, Applicant submitted an indirect comparison of the claimed compounds, namely, the four 2-ethyl-19-nor compounds claimed and the four 2-ethylidene-19-nor compounds claimed, versus the prior art compounds disclosed in the

above two references, namely, the 2-methyl-19-nor compounds and the 2-methylene-19-nor compounds, respectively. Applicant did this by comparing the intestinal transport activity and bone calcium mobilization activity data disclosed in the '410 and '928 references with the intestinal calcium transport activity and bone calcium mobilization activity data disclosed in Applicant's specification. More specifically, the intestinal calcium transport activity and bone calcium mobilization activity of the claimed compounds and the prior art compounds were both compared to the standard vitamin D compound, namely, $1\alpha,25$ -dihydroxyvitamin D_3 which is the natural hormone commonly used as the standard against which all other vitamin D compounds are compared. Applicant showed that the intestinal calcium transport activity and bone calcium mobilization activity of the presently claimed compounds was different than the intestinal calcium transport activity and bone calcium mobilization activity of the prior art compounds with respect to $1\alpha,25$ -dihydroxyvitamin D_3 . Accordingly, Applicant concluded that even though the instantly claimed compounds have a close structural similarity to the prior art compounds, their biological activities were significantly different from what one would have expected based solely on structural similarities. Based on this indirect comparison, Applicant requested the Examiner to withdraw the §103 obviousness rejection based on the '410 and '928 references.

The Examiner, however, rejected Applicant's comparison of intestinal calcium transport activity and bone calcium mobilization activity indicating that this comparison was not a true side-by-side comparison because it did not compare the closest prior art compounds to the instantly claimed compounds, and did not do so under identical conditions. The Examiner concluded that since the comparison was not a true side-by-side comparison, it did not refute the prima facie case of obviousness set forth by the Examiner. Applicant, however, respectfully disagrees for the following reasons.

First, Applicant believes it has compared the closest prior art compounds to the instantly claimed compounds. More specifically, claims 1 and 2 herein claim 2α and 2β -ethyl-19-nor- $1\alpha,25$ -dihydroxyvitamin D_3 . The '410 reference discloses 2α and 2β -

methyl-19-nor-1 α ,25-dihydroxyvitamin D₃ and the biological data for such compounds are disclosed in Table 1 at columns 15 and 16 of the '410 reference. Thus, the only difference between the instantly claimed compounds and the prior art compounds is that the instantly claimed compounds claim a 2-ethyl derivative whereas the prior art compounds disclose a 2-methyl derivative. These are clearly adjacent homologs, and Applicant cannot see how one could not consider these compounds to be the closest prior art compounds to what Applicant is claiming in claims 1 and 2. Every moiety is identical with the exception of the 2-position, and thus Applicant believes the 2-methyl compounds disclosed in the '410 reference are the closest prior art compounds.

The same is true of the compounds claimed in claims 3 and 4 herein. These compounds are identical to those claimed in claims 1 and 2 except that they are the 20(S) derivatives thereof. The '410 reference also discloses the 20(S) analogs of the 2-methyl compounds and the biological data for these compounds are disclosed in Table 1 of the '410 reference. Thus, once again, the only difference between the compounds claimed in claims 3 and 4 and the prior art compounds is that at the 2-position of the A ring, the present compounds are 2-ethyl compounds whereas the prior art compounds are 2-methyl compounds. Once again, Applicant believes the 20(S) 2-methyl compounds of the prior art are the closest prior art compounds to the 20(S) 2-ethyl compounds claimed herein.

The same analysis can be made with respect to present claims 5-8 and the prior art compounds in the '928 reference. The prior art '928 reference discloses 2-methylene-19-nor-1 α ,25-dihydroxyvitamin D₃ and the 20(S) derivative thereof. The only difference between those prior art compounds and the presently claimed compounds in claims 5-8 is that the presently claimed compounds are 2-ethylidene compounds rather than 2-methylene compounds. Thus, once again, the presently claimed compounds are the next adjacent homologs of the prior art compounds. Thus, Applicant believes the compounds disclosed in the prior art '928 reference are clearly the closest prior art compounds to the presently claimed compounds set forth in claims 5-8.

In Applicant's view, it is clearly comparing the instantly claimed compounds to the closest prior art compounds. If the Examiner believes there is a compound that is structurally closer to Applicant's claimed compounds than those disclosed in the '410 and '928 references, Applicant would appreciate being so advised so that Applicant can provide a comparison of biological data for the Examiner. However, from the Applicant's viewpoint, it appears that Applicant is in fact analyzing and dealing with the closest prior art compounds.

Next, the Examiner indicates that Applicant's indirect comparison is not acceptable since it is not a true side-by-side comparison performed under identical conditions. However, the Examiner should be aware that the in vivo intestinal calcium transport activity and bone calcium mobilization activity data were prepared and performed in the same manner for Applicant's instantly claimed compounds as the prior art compounds taught in the '410 and '928 references. First, the Examiner should note that both prior art references as well as the instantly filed patent application have identical inventors, namely, Hector F. DeLuca and Rafal R. Sicinski. These inventors have numerous patents and they consistently report intestinal calcium transport data as per the well-known everted sac technique and serum calcium data via the use of atomic absorption spectrometry. The data obtained in the prior art '928 and '410 references was determined in the identical manner as the data obtained and reported in Table 1 at pages 23-24 of the present specification. More specifically, the Examiner should note that the technique utilized of providing a relatively normal calcium diet for one week and then switching the animals to a low calcium diet in order to deplete the animal's blood serum of calcium is identical. The only exception is that in the '410 and '928 references, the low calcium diet is fed for two weeks rather than being fed for three weeks in the experiment reported in the present specification. However, this difference is insignificant for purposes of obtaining the calcemic data reported. The techniques are set forth in the '410 reference at column 16, line 55 through column 17, line 32. In the '928 reference, the techniques utilized are set forth at column 16, line 57 through column 17, line 33. In the present

specification, the same technique is set forth in the paragraph immediately following Table 1 on page 24. Thus, as the Examiner can see, the data is obtained utilizing substantially the same techniques and regimen. A Declaration by the inventors can be supplied supporting this conclusion if the Examiner so requires.

The Examiner should further note that the U.S. Patent Office has specifically accepted indirect comparisons between the claimed invention and the closest prior art as being probative of non-obviousness. Applicant refers the Examiner to page 700-147 in section 716.02(b) of the MPEP. In that section, the following is stated:

“Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re Boesch*, 617 F2d 272, 205 USPQ 215 (CCPA 1980) and MPEP §716.02(d)-§716.02(e). See *In re Blondel*, 499 F2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and *In re Fouche*, 439 F2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a prima facie case of obviousness.”

Applicant also encloses a copy of page 700-147 of the MPEP and further includes copies of the *In re Blondel* and *In re Fouche* references cited above. Of these two references, *In re Blondel* is particularly relevant. In that case, the Patent Office rejected evidence submitted by the Applicant as not comparing the claimed compound to the closest prior art. However, the Applicant referred to two previous affidavits wherein both compounds are compared to a standard which in that case was fluphenazine enanthate. More specifically, Applicant stated that the claimed compound has a duration of activity greater than fluphenazine enanthate, while the prior art compound had a duration of activity substantially the same as fluphenazine enanthate. While the Patent Office was not impressed with the Applicant's indirect comparison, the CCPA was, and held that such an indirect comparison was adequate to refute the Examiner's prima facie case of obviousness. Applicant would like to refer the Examiner specifically to the second column on page 1067 through the first column on page 289 of the *In re Blondel* case.

Thus, Applicant believes it has adequately shown via the Amendment dated February 18, 2003 that Applicant's compounds have distinct biological activity from the prior art compounds of the DeLuca et al '410 patent and the DeLuca et al '928 patent. Although the evidence is indirect, it clearly provides a detailed, step-by-step analysis of the evidence in support of the conclusion that, even though the instantly claimed compounds are structurally similar to the prior art compounds of the '410 and '928 patents, the biological activities of Applicant's claimed compounds are different and unexpected as compared to the prior art compounds. Applicant believes this indirect comparison is persuasive and provides adequate probative evidence of nonobviousness.

As a result, Applicant believes the Examiner should withdraw the rejection of claims 1-56 under 35 USC §103(a).

In the Office Action, the Examiner rejected claims 1-4 and 9-32 under the doctrine of obviousness type double patenting as being unpatentable over claims 1, 2, 7 and 12-20 of the '410 reference. The Examiner indicated that since the present application claimed a homolog of the compound exemplified in the '410 patent, it would be expected that homologs would have the same properties and thus have similar uses as taught by the '410 reference.

However, as discussed previously herein, the compounds of claims 1-4 and 9-32 do not have the same properties as the compounds claimed in the '410 patent. Thus, as stated by the Examiner, since the compounds of claims 1-4 are homologs of the compounds disclosed in the '410 patent, one would expect their activities to be substantially the same. However, as noted above, these activities are not substantially the same resulting in the compounds of claims 1-4 not being obvious in view of the compounds disclosed in the '410 patent. Thus, Applicant requests the Examiner withdraw the obviousness type double patenting rejection of claims 1-4 and 9-32.

In the Office Action, the Examiner rejected claims 5-8 and 33-56 under the doctrine of obviousness type double patenting as being unpatentable over claims 1, 2, 7

Application No. 09,871,227
Amendment Dated July 16, 2003
Reply to Office Action of April 25, 2003

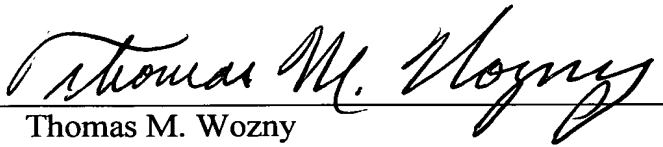
and 12-16 of the '928 reference. The Examiner indicated that since the present application claimed a homolog of the compound exemplified in the '928 patent, it would be expected that the homologs would have the same properties and thus similar uses as taught by the '928 reference.

However, as discussed previously herein, the compounds of claims 5-8 and 33-56 do not have the same properties as the compounds claimed in the '928 patent. Thus, as stated by the Examiner, since the compounds of claims 5-8 are homologs of the compounds disclosed in the '928 patent, one would expect their activities to be substantially the same. As noted above, however, these activities are not substantially the same resulting in the compounds of claims 5-8 not being obvious in view of the compounds disclosed in the '928 patent. Thus, Applicant requests the Examiner withdraw the obviousness type double patenting rejection of claims 5-8 and 33-56.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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range does not exceed 1.3 and that over fifty per cent of this range is claimed by appellants. The smooth continuum represented by the curve contradicts the majority's conclusion that appellants' invention produces a difference in kind (unexpected results) rather than degree.

I agree with the board that it would be obvious to a person of ordinary skill in the art with Reiling before him to optimize the intensity of white light emission by choosing from among ratios between halogen atoms and mercury atoms.

I would affirm.

Court of Customs and Patent Appeals

In re BLONDEL, FOUCHE, AND GUEREMY

No. 9150 Decided June 27, 1974

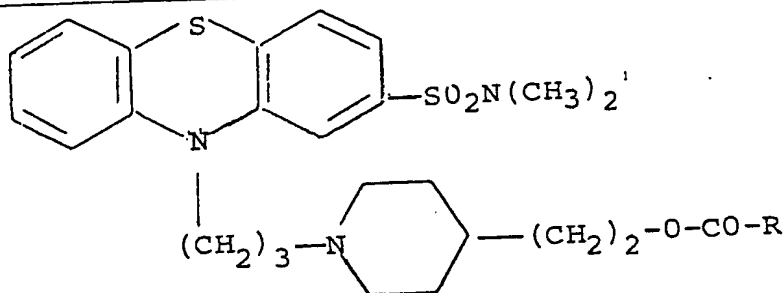
PATENTS

1. Patentability — Composition of matter (§51.30)

Claims are allowed where indirect comparison shows that claimed compounds possess a duration of activity greater than would be reasonably expected by one skilled in the art from a knowledge of performance of prior art compounds; even if claimed compounds were structurally obvious, evidence overcomes prima facie case of obviousness.

Particular patents—Phenthiazine

Blondel, Fouche, and Gueremy, Phenthiazine Derivatives, claims 1 and 3 to 6 of application allowed.



wherein R represents an alkyl,¹ alkenyl² or alkynyl³ group having 7-17 carbon atoms. Claim 3 further limits R to specific alkyl, alkenyl, or alkynyl groups. Claims 4-6 are to

¹ The dimethyl sulfamoyl group.

² Open-chained hydrocarbon radical, C_nH_{2n+1} .

³ Open-chained hydrocarbon radical, C_nH_{2n-1} .

⁴ Open-chained hydrocarbon radical containing a triple bond.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Jean-Claude Rene Georges Blondel, Jean Clement Louis Fouche, and Claude Georges Alexandre Gueremy, Serial No. 717,012, filed Mar. 28, 1968; Patent Office Group 121. From decision rejecting claims 1 and 3 to 6, applicants appeal. Reversed.

ELLSWORTH H. MOSHER and STEVENS, DAVIS, MILLER & MOSHER, both of Arlington, Va., for appellants.

JOSEPH F. NAKAMURA (FRED E. McKELVEY of counsel) for Commissioner of Patents.

Before MARKEY, Chief Judge, and RICH, BALDWIN, LANE, and MILLER, Associate Judges.

RICH, Judge.

This appeal is from the decision of the Patent Office Board of Appeals affirming the examiner's rejection of claims 1 and 3-6 of application serial No. 717,012, filed March 28, 1968, for "Phenthiazine Derivatives," on the ground of obviousness in view of prior art, under 35 U.S.C. 103. We reverse.

The issues are whether the claimed invention is prima facie structurally obvious and, if so, whether there has been a sufficient showing of unexpected advantageous properties to overcome prima facie obviousness.

The Invention

The invention, a new group of chemical compounds, will be understood from the claims on appeal. Claim 1 reads:

1. A phenthiazine derivative of the formula:

species within the scope of claims 1 and 3. These derivatives are said to be long-acting neuroleptics, antiemetics and tranquilizers.

The References

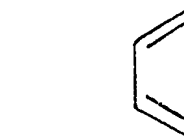
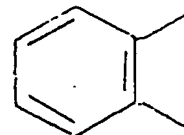
The references relied on are:

British patent 904,208 Aug. 22, 1962

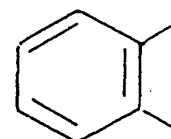
Yale et al. I 3,194,733 July 13, 1965

Yale et al. II 3,350,268 Oct. 31, 1967

The British patent assignee of the phenthiazine derivative



The Patent Office structurally close compounds. It is patent where X is moyl but this co



wherein X can include trifluoromethyl, higher alkyl, alkynyl, and R is alkyl, "higher alkyl," as employed by straight and branched than five carbon compounds have 6- that:

The compounds are therapeutically utilizable as agents. The corresponding derivatives or that they are when admini

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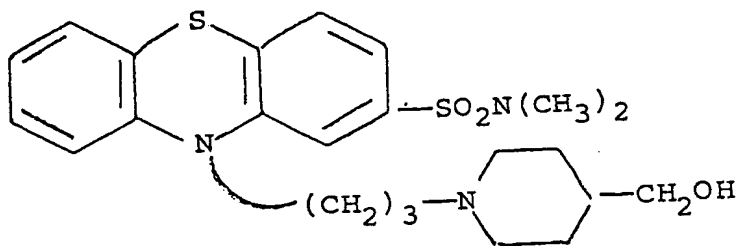
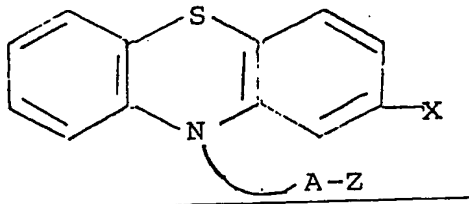
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The British patent to Rhone-Poulenc S.A., assignee of the present application, discloses phenthiazine derivatives having the formula

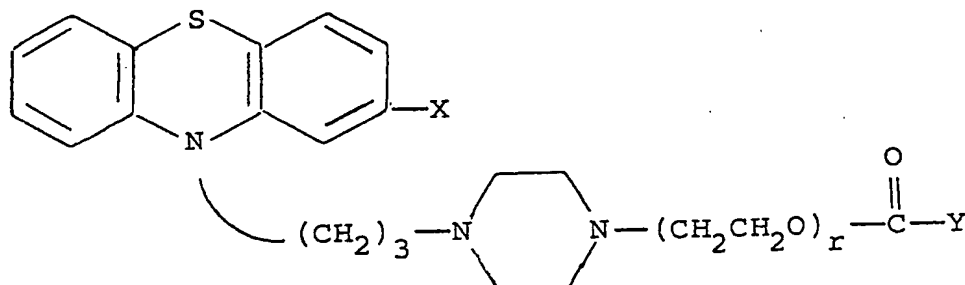


The Patent Office regards this compound as structurally closest to appellants' claimed compounds. It is the only species of the British patent where X represents dimethylsulphamoyl but this compound differs from appel-

wherein X is a dimethylsulphamoyl group, as in appellants' compounds; A is, inter alia, a $-(CH_2)_3$ -group; and Z can be a piperidino group having substituted thereon a group of the formula $-C_nH_{2n}OR$, where n is 2 and R is a hydrogen atom or a carboxylic acyl group. These derivatives are disclosed as very active sedatives and antiemetics, in some cases having analgesic activity. Example XIV of the patent discloses the preparation of 3-dimethylsulphamoyl-10-[3-(4-hydroxymethyl-1-piperidyl)propyl]-phenthiazine, which has the formula:

lants' claimed compounds as stated hereinafter.

Yale I, and Yale II which is treated by the Patent Office as cumulative, discloses "phenthiazines" of the general formula:



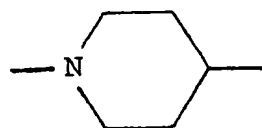
wherein X can be various organic radicals, including trifluoromethyl, $-CF_3$, Y may be higher alkyl, higher alkenyl, or higher alkynyl, and r is 1 or 2. The terms "higher alkyl," "higher alkenyl" and "higher alkynyl," as employed by the patentees, include both straight and branched chain radicals of more than five carbon atoms. The preferred compounds have 6-14 carbon atoms. Yale I states that:

The compounds of this invention are therapeutically active substances which are utilizable as tranquilizing (or ataractic) agents. These compounds differ from the corresponding lower alkanolic acid ester derivatives or the free hydroxyl derivatives in that they are significantly longer acting when administered parenterally and thus,

when injected subcutaneously, for example, in a suitable vehicle, yield a long acting tranquilizing drug. [Emphasis ours.]

The Rejection

The claims stand rejected for obviousness under 35 U.S.C. 103 on the British patent in view of Yale I and II. The board held that the British patent "encompassed" the claimed



compounds in its generic disclosure and that the compound of Example XIV, when taken with the generic disclosure, most closely approaches the claimed invention, the patent making it clear that hydroxymethyl and hydroxyethyl compounds are considered equivalent. The board felt it is clear that the British patent "contemplates all carboxylic acyl esters," while admitting there is no specific teaching of a long chain acyl esterifying group, and that it would be obvious to increase the duration of activity by preparing an ester with a long chain acid in view of the Yale patents, particularly Yale I, which discloses the selection of long chain carboxylic acyl groups to esterify alkylol-substituted phenothiazines related to the British patent and to phenothiazines of the structure claimed. The board said Yale I states that longer lasting activity is produced where longer chain carboxylic acyl esterifying groups are introduced. The board's reason for agreeing with the examiner's holding of obviousness is summed up as follows:

It is clearly stated that longer lasting activity for the same purpose is produced where longer chain carboxylic acyl esterifying groups are introduced. It would thus be clearly obvious to the organic chemist to increase the duration of activity in the class of compounds taught in the British patent to select as the generically disclosed carboxylic acyl group a long chain group, thus anticipating [sic] appellants' claimed compounds.

Commenting on the affidavits or declarations, designated Garret I and Garret II, filed by appellants to show advantages in their products in the form of a quantitatively unexpected increase in the duration of activity, the board said:

The declarations, in our opinion, do not demonstrate any unexpected properties in the now claimed compounds. As indicated in Yale et al., longer activity is to be expected in longer chain esters. The declarations demonstrate little more than that. The reference compounds and the herein claimed compounds appear to be useful for substantially the same purposes, and the comparative showing of somewhat longer activity in a single area of a community of pharmaceutical activities does not persuade us of unobviousness of the selected members of the class depicted in the British patent for the same utility.

Appellants' Position

Appellants' position is, first, that the invention is not structurally obvious since the British patent disclosure, although perhaps generic to the invention, does not specifically teach appellants' subgenus and there is no reason why one skilled in the art would select that

subgenus from the at least 384 genera encompassed within the broad general formula of the British patent. Appellants agree that the closest disclosure of the British patent is Example XIV, but point out that this compound differs from the claimed compounds in that it is an alcohol, not an ester, and that it is not the alcohol from which the claimed ester subgenus is derived since the alcoholic hydroxy group is joined to the piperidino ring through a methylene group, $-\text{CH}_2-$, not an ethylene group, $-\text{CH}_2\cdot\text{CH}_2-$. Appellants further point out that Yale's structural formula differs from appellants' subgenus in that Yale does not disclose that the substituent X may be dimethyl sulphamoyl⁶ and the heterocyclic ring joining the ester group to the phenothiazine nucleus is a piperazine ring⁷ in Yale, not a piperidine ring⁸ as in the compounds of the invention.

Assuming, arguendo, that the claimed compounds are structurally obvious in view of the British patent, in case that point is ruled against them, appellants contend that this would not compel a finding of obviousness under § 103 if they have shown unexpected advantageous properties in their new compounds. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); *In re Papesch*, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (1963). They say this is so even though the utility of their compounds is in the same field as the utility of the prior art compounds if their compounds are substantially greater in effectiveness. *In re Lohr*, 50 CCPA 1274, 317 F.2d 388, 137 USPQ 548 (1963); *In re Wiechert*, 54 CCPA 957, 370 F.2d 427, 152 USPQ 247 (1967); *In re Risse*, 54 CCPA 1495, 378 F.2d 948, 154 USPQ 1 (1967). They further contend that even though Yale may suggest that duration of activity of the compounds of the British patent may be extended by forming esters thereof with higher rather than lower acids, whereby the number of carbon atoms in the R group is increased, their compounds are nevertheless unobvious and patentable if their proofs show, as they contend they do, that the increase in duration of activity is greater than those skilled in the art would have any reason to expect.

Opinion

On the entire record, we agree with appellants that they have established unobviousness

⁶ See note 1, supra.

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⁸ See note 5, supra.

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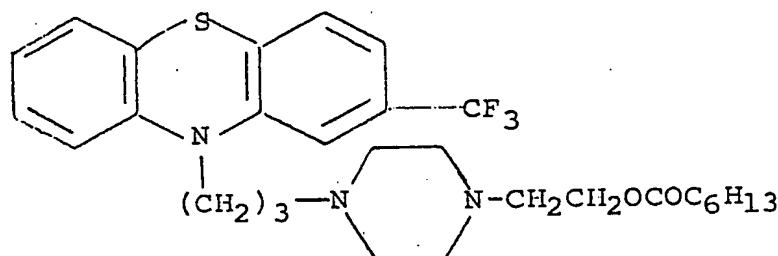
182 USPQ

of their claimed compounds over the disclosures of the references.

The key consideration on the question of unobviousness is the duration of the activity of the invention compounds in certain tests which were performed on them as antiemetics administered to dogs (anti-apomorphine activity). Garret I, the first affidavit evidence submitted by appellants, established the superior duration of the activity of the invention compounds, in which the R substituent contains from 7 to 17 carbon atoms, relative to a Yale compound named "fluphenazine enanthate," an ester wherein the R group contains 6 carbon atoms. These tests were made on 14 of appellants' compounds. They showed all of the compounds tested to be superior in duration of activity to fluphenazine enanthate but were

not accepted by the examiner as showing unobviousness and were criticized by him as not showing that the prolongation of activity was other than would have been expected from Yale's disclosure, and as not having compared the closest prior art, namely, the sulfamoyl compound of British patent Example XIV (an alcohol) and its esters.

Appellants responded by submitting a second affidavit, Garret II, reporting on comparative tests on certain compounds, designated I, II, III, and IV, in which they undertook to show what one skilled in the art would expect from a knowledge of the references and that the invention compounds exceed that expectation. Compound I was fluphenazine enanthate, one of Yale's preferred compounds, which has the formula



It will be noted that what corresponds to R in appellants' claimed compounds, limited to those in which R contains 7-17 carbon atoms, contains 6 carbon atoms, i.e., the $-C_6H_{13}$ group. Garret II is first concerned with showing what increasing the number of those carbon atoms would be expected to do by way of prolonging the effectiveness of the drug as an antiemetic.

Compound II was fluphenazine decanoate, the same as compound I except that R is $-C_{10}H_{21}$. This too is one of the compounds disclosed by Yale, who suggests that R (or Y, as he designates it) should have from 6 to 14 carbon atoms, preferably 9 to 14. Appellants' tests on compounds I and II of Yale's series of trifluoromethyl ($-CF_3$) compounds led the declarant Garret to conclude that the duration of activity of compounds I and II is of a similar order and not significantly affected by the number of carbon atoms in the R residue, that is by the increase from C_6 to C_{10} in R.

Next, to meet the objection that appellants had not compared their compounds to the closest prior art, deemed to be British patent Example XIV and its esters, Garret tested compound III which was the heptanoic acid ester of British Example XIV, the R portion of which contains 6 carbon atoms. This compound had a duration of activity very similar to compounds I and II. Of the three, com-

pound II (C_{10} in R) was somewhat better than the other two, but not significantly so.

Compound IV tested by Garret is a compound of the invention, corresponding to the formula of claim 1, wherein R is $-C_9H_{19}$, and which contains the dimethyl sulfamoyl group as did compound III. The results of the tests of the four compounds, given in both tabular and graph form in the affidavit, show that compound IV had a prolongation of activity very much greater than one would have expected on the basis of knowledge of the effect of increasing the number of carbon atoms in the R group of the Yale compounds I and II from 6 to 9. The increase in the prolongation of activity in appellants' series of compounds, in going from 6 to 9 carbons in the R group, is, according to their calculations, unchallenged by the Patent Office, about 150% in excess of the reasonable expectation.

The board was nevertheless critical of appellants' tests, saying:

The declaration does not compare Compound III, representative of the British patent, with an ester containing an R group of 7 carbon atoms each included in claims 1 and 3, but compares a longer chain ester having 9 carbon atoms in the R grouping. This comparison, in our opinion, is insufficient since it does not compare the

shortest chain compound now claimed with a representative reference compound. We have no reason to believe that a 7-carbon R group compound exhibits more than the expected increase in activity over the 6-carbon R group compound * * *. [Emphasis ours.]

It is with respect to this objection that appellants assert that the information the board found lacking is in fact available by an indirect comparison of data of record. They state this argument in summary fashion as follows:

In Garret I the C₇ compound is shown to have a duration of activity considerably in excess of fluphenazine enanthate. In Garret II the C₆ compound [compound III] is shown to have substantially the same duration of activity as fluphenazine enanthate [compound I]. Since Garret II describes tests carried out under substantially identical conditions to those of Garret I, it is possible to get a reliable indication of the duration of activity of the C₇ compound and of the other invention compounds described in Garret I compared to the C₆ compound indirectly by comparing the duration of activity of each of the compounds under consideration with fluphenazine enanthate.

[1] We have heretofore approved such indirect comparison in *In re Fouche*, 58 CCPA 1086, 439 F.2d 1237, 169 USPQ 429 (1971), upon which appellants rely. We note that the solicitor has not challenged our holding in *Fouche* or attempted to answer appellants' arguments based thereon but has merely asserted that appellants should have made a direct comparison. Appellants' brief goes through a detailed, step-by-step analysis of the evidence in support of the conclusion to be drawn from the indirect comparison, which we will not undertake to repeat. Suffice it to say that we find it persuasive that the claimed compounds possess a duration of activity that is greater than would be reasonably expected by one skilled in this art from a knowledge of the performance of the prior art compounds.

We find nothing of record to indicate that workers in this field recognize the kind of predictability which the Patent Office seems to have taken for granted. On the contrary, we note the introductory statement in the British patent says:

It has * * * been demonstrated that of the very large number of possible N-substituted phenothiazine compounds that have been proposed or tested by various workers, only comparatively few types have useful application in human or veterinary medicine and that both the nature and the degree of useful effect can radically alter even with apparently small changes in chemical structure.

We also note that Yale was not speaking, when commenting on the effect of the use of

higher rather than lower acid ester derivatives, of phenothiazines in general or of the phenothiazines of the British patent (which are inclusive of appellants' compounds) but of "The compounds of this invention," meaning his own group, which have several "small changes in chemical structure" from appellants' compounds, as pointed out above. The evidence shows that with the latter the effect of increasing the number of carbon atoms in the R group is quantitatively quite different from the effect of increasing the number of carbon atoms in the corresponding group in the Yale series of compounds. We feel that appellants' disclosures contribute something unobvious to the knowledge in this art and that their claims are commensurate with that contribution. We therefore reverse the rejection under § 103.

This conclusion with respect to the showing of a prolongation of the duration of activity beyond what could reasonably be expected by the man of ordinary skill in the art makes it unnecessary for us to pass on the issue of whether appellants' claimed compounds are structurally obvious since, even if they are, the prima facie case which that would make for the Patent Office has been overcome by the evidence introduced by appellants. In re Papesch, supra.

The decision of the board is reversed.

Court of Customs and Patent Appeals

In re SCARBROUGH

No. 9249

Decided June 27, 1974

PATENTS

1. Court of Customs and Patent Appeals — Record (\$28.30)

Specification — Reference to other disclosures (\$62.5)

Patent issued after applicant's filing date cannot be relied on as evidence to show that applicant's specification is enabling; court grants Commissioner's motion to strike patent from record.

2. Court of Customs and Patent Appeals — Briefs (\$28.05)

Argument of counsel that Board was wrong in concluding that disclosure is insufficient cannot take place of evidence lacking in the record.

3. Specification — Sufficiency of disclosure (\$62.7)

Disclosure is insufficient where an unreasonable amount of work would be required

to arrive at detail; applicant says that

Particular patent
Scarborough. C
Response, claims
cation refused.

Appeal from Bo
Office.

Application of
Scarborough, Seria
1968; Patent Office
rejecting claims 1
appeals. Affirmed

NATHAN CASS, F
lant.

JOSEPH F. NAKA
counsel) for Co

Before MARKEY
BALDWIN, LA
Judges.

LANE, Judge.

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filtration. There appears to be no dispute that appellant's compositions in fact possess this property or that it is advantageous. The issue is whether it would be unexpected in view of Wei.

The Patent Office takes the position that compositions made according to Wei's teachings are initially clear and require no filtration. Portions of the Wei patent would seem to support such a view. Wei's object is to produce clear aqueous solutions containing lanolin. After explaining how to select and mix the various ingredients, the patentee states:

The resulting composition may exhibit some cloudiness or haziness, which is primarily due to impurities in the lanolin wax. These impurities may be removed by any technique suitable for solid-liquid phase separation. It has been found that the cloudiness may be removed easily by a filtration step wherein the liquid is filtered on a filter cloth or press. The resulting filtrate is a clear, sparkling transparent liquid having the lanolin in solution.

This passage would indicate that cloudiness occurs only in some instances and that it is due to solid impurities in the lanolin.

Wei, however, gives twelve working examples. In all but the first, a filtration step is expressly taught. In the first example solid lanolin is used, whereas the appealed claims call for a liquid fraction of lanolin. As regards the use of liquid lanolin, Wei gives no example purporting to obtain a clear solution without filtration.

We believe that one skilled in the art would have concluded from the totality of the Wei patent either (1) that initially clear solutions could not be obtained at all using a liquid fraction of lanolin; or (2) that clear solutions could not be consistently obtained by Wei's teachings. Our belief is further supported by appellant's affidavits, which describe experiments corresponding to the single example of Wei in which filtration is not mentioned. The affidavits state that cloudy solutions were obtained.

In view of the uncertainty generated by the Wei patent, the initial cloudiness obtained with Wei's teaching at a 10:1 ratio of alkylamide to lanolin, and Conrad's teaching of better clarity with 6:1 and 9:1 ratios of surfactant to lanolin than with 3:1, we agree with appellant that it would have been completely unexpected that by using *less* solubilizer and *less* surfactant, clear solutions would be consistently obtained without filtration. The fact that appellant's compositions consistently eliminate the need for filtration is an unexpected advantageous property not pos-

sessed in general by the class of compositions taught by Wei nor by any specific composition disclosed in the prior art of record. Accordingly, despite the fact that some of the claimed compositions are within the broad teachings of Wei, we conclude that because of their unexpected advantageous property they would not have been obvious.

The decision of the board is reversed.

Court of Customs and Patent Appeals

In re Fouché

No. 8484

Decided Apr. 22, 1971

PATENTS

1. Abandonment — Application (§10.3)

Specification — Reference to other disclosures (§62.5)

Abandoned applications less than 20 years old can be incorporated by reference to same extent as copending applications; both types are open to public upon referencing application issuing as a patent.

2. Specification — Reference to other disclosures (§62.5)

Reference in sole application to "Example I of our application No. _____" was reasonably precise since (1) it would be unreasonable to read quoted language as pertaining to anything but an earlier or concurrently filed United States application, (2) applicant at time of filing instant application had on file in Patent Office an application containing enough information to complete his disclosure, (3) such other application contains an Example I disclosing involved method, and (4) there existed no other application to which referring language could have pertained; therefore, amendment specifying serial number and date of such application did not introduce new matter.

3. Specification — Sufficiency of disclosure (§62.7)

Inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention; nevertheless, applicant must use some technique of providing teaching of how to use which is commensurate with breadth of protection sought by

claim, unless such knowledge is already available to persons skilled in the art; thus, where applicant undertakes to define invention by recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of group.

4. Patentability — Utility (§51.75)

Specification — Sufficiency of disclosure (§62.7)

Patent Office's doubt that compositions would be useful can lead not only to a rejection under 35 U.S.C. 101, but also to a rejection under how-to-use provision of section 112, since, if compositions are useless, specification cannot have taught how to use them.

5. Pleading and practice in Patent Office — Rejections (§54.7)

Patent Office's doubts as to truth of specification's teaching that compounds are useful for therapeutic purposes being reasonable, applicant has burden to show truth of teaching.

6. Specification — Sufficiency of disclosure (§62.7)

35 U.S.C. 112 does not require that all compositions within a claim have same degree of utility.

Particular patents—Derivatives

Fouche, Dibenzoheptadiene Derivatives, claims 2 and 3 of application allowed; claim 1 refused.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Jean Clement Louis Fouche, Serial No. 463,936, filed June 14, 1965; Patent Office Group 120. From decision rejecting claims 1 to 3, applicant appeals. Affirmed as to claim 1; reversed as to claims 2 and 3.

JOHN F. WITHERSPOON and HAROLD C. WEGNER (STEVENS, DAVIS, MILLER & MOSHER of counsel) all of Arlington, Va., for appellant.

S. WM. COCHRAN (RAYMOND E. MARTIN and HENRY W. TARRING II of counsel) for Commissioner of Patents.

Before RICH, ALMOND, BALDWIN, and LANE, Associate Judges, and RE, Judge, United States Customs Court, sitting by designation.

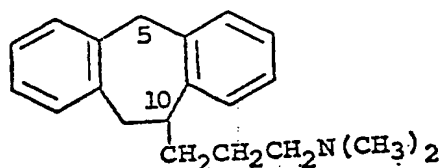
LANE, Judge.

This appeal is from the decision of the Patent Office Board of Appeals affirming the rejection of claims 1-3 in appellant's application serial No. 463,936, filed June 14, 1965, for "Dibenzoheptadiene Derivatives." No claims have been allowed. We affirm as to claim 1 and reverse as to claims 2 and 3.

The invention claimed is a class of compounds having pharmaceutical utility due to their antidepressant, neuroleptic and tranquilizing properties. Claim 3 is illustrative of the appealed claims since it is drawn to the compound closest to the prior art of all the compounds within the appealed claims.

3. 10-(3-dimethylaminopropyl) dibenzo [a,d] cycloheptadiene and its acid addition salts and quaternary ammonium derivatives.

10-(3-dimethylaminopropyl) dibenzo [a,d] cycloheptadiene has the following structural formula:



Sufficiency of Disclosure—Incorporation by Reference

The first issue to be decided is whether the claims are adequately supported under the first paragraph of 35 U.S.C. 112, specifically, the how-to-make requirement. The instant specification contains no express teaching of how to make 10-(3-dimethylaminopropyl) dibenzo [a,d] cycloheptadiene, which is claimed in claim 3 and is a starting material for making other compounds covered by the claims. The specification does, however, state that the compound can be "prepared as described in Example I of our application No. _____". No other identification of the referenced application was given at the time the instant application was filed. Appellant later attempted, by amendment, to change the referring language from "our application No. _____" to "my Application Serial No. 459,921 filed May 17, 1965." The Patent Office did not assign this serial number to the earlier application until after the instant application was filed.

The examiner, while recognizing that a patent applicant may complete his disclosure, and hence satisfy 35 U.S.C. 112, by reference to an earlier or concurrently filed U. S. appli-

cation, took the referring language in the amendment. There is no suggestion sought to be enough information for specification claims. The here is where the language was added by reference.

The law is to the contrary, and so Patent Law 70 Annual parte Harvey 1968), in which the language adequate and serial which the beneficiary's docket a means of i-

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Example I of the instant application which from all of our no "new" reference entered would amount to a new invention.

The Patent Office in the application reasons for

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cation, took the view that the original referring language was defective and hence that the amendment introduced new matter. There is no dispute that the application sought to be incorporated actually contains enough information to complete the instant specification so as to support the appealed claims. The sole issue on the § 112 rejection here is whether the original referring language was adequate to effect an incorporation by reference.

The law on this question is succinctly set forth, and some of the authorities reviewed, in Patent Law Perspectives, § A.5[1] [a] (1969-70 Annual Review). After discussion of *Ex parte Harvey*, 163 USPQ 572 (P.O. Bd.App. 1968), in which the board held reference language adequate even though the filing date and serial number were not given, but in which the board also suggested that the attorney's docket number should have been used as a means of identification, the authors state:

[I]t seems amply clear that an applicant should be permitted to incorporate the disclosure of a copending application whether or not an attorney's docket number is provided in the referencing application so long as the reference application is sufficiently well identified to distinguish it from all others.

The question to be decided here is, therefore, whether the language "our application No. _____" together with the reference to Example I thereof, distinguished the application which later received serial No. 459,921 from all others. If it did, there can of course be no "new matter" problems, since the amendment entering the serial number and filing date would amount to a mere change in wording.

The Patent Office position is that the language in question did not uniquely identify the application sought to be incorporated. Its reasons for this position are:

a. The use of the word "our" would suggest that a joint application was intended, and serial No. 459,921 is a sole application.

b. There is nothing in the referring language which would exclude the possibility that a foreign application was intended.

c. There is nothing in the referring language which would exclude the possibility that a later-to-be-filed application was intended.¹

[1] The solicitor has also pointed out that the reference language could also have pertained to an already abandoned application. This factor, however, is of little significance, since already-abandoned applications less than twenty years old can be

Appellant counters these reasons with the following arguments:

a. The use of the word "our" was an obvious slip of the tongue, arising from the fact that in most countries application for a patent is made in the name of the assignee. (Apparently it is customary to refer to a corporate assignee in the plural number.)

b-c. It is unreasonable to conclude that a foreign or later-filed application was intended, since an applicant could obviously derive no benefit, under United States law, from incorporating a foreign or later-filed application by reference.

Appellant further urges that he was led to employ the procedure used here by the Manual of Patent Examining Procedure, § 608.01(p) of which then provided, in part:

If a concurrently or previously filed application of the same inventor adequately discloses the preparation of the starting material, amendments to include reference to such application by serial number and a general method of preparation are proper.

Appellant views this provision as permitting incorporation by reference by amendment even where the originally filed application contained no attempt whatever to incorporate another application. He argues that the Patent Office should not be permitted to change its position and apply the new position against him, after he was led astray by its first position. We need not decide the merits of appellant's contention in this regard, since we find the board's decision on the § 112 rejection reversible on the considerations previously mentioned.

[2] While the board was undoubtedly correct in pointing out that appellant could have used a more precise identification technique in referring to the earlier application, and while the solicitor is correct in pointing out that the technique used does not absolutely distinguish the application sought to be referenced from all other possible applications, we find that the identification was reasonably precise.

First, there is some merit to appellant's rebuttal arguments, supra, that it would be unreasonable to read the referring language as pertaining to anything but an earlier or concurrently filed United States application.

Second, it is undisputed that, at the time of filing the present application, appellant in fact had on file in the Patent Office an appli-

incorporated by reference to the same extent as copending applications. Both types are open to the public upon the referencing application issuing as a patent. (Rule 14(b)).

cation containing enough information to complete his disclosure as to the appealed claims. It is therefore clear that he had solved, as of his present filing date, any technical problems involved in making and using the claimed compositions. This is a major consideration in judging compliance with the first paragraph of § 112. See *In re Argoudelis*, 58 CCPA _____, 434 F.2d 1390, 168 USPQ 99 (1971), and especially Judge Baldwin's concurring opinion therein.

Third, application serial No. 459,921 does in fact contain an "Example I" disclosing a method for preparing 10-(3-dimethylaminopropyl) dibenzo [a,d] cycloheptadiene. We note that in *Ex parte Harvey*, supra, the board looked to the nature of the subject matter disclosed in the earlier application as one means of linking that application to the referring language.

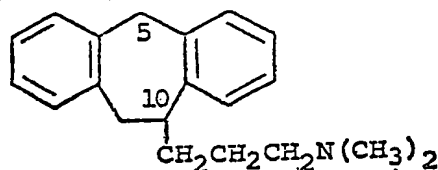
Fourth, there has been no showing by the Patent Office that there existed any other application to which the referring language could have pertained.

For these reasons we hold that the language employed in the present application adequately incorporated the disclosure of previously filed application serial No. 459,921 by reference and hence that the amendment to specify the serial number and filing date did not introduce new matter into the specification. In view of the result we have reached on this point, we need not consider appellant's alternative argument that the method of preparing the compounds in question was within the skill of the art and not required for support of the claims.

Obviousness

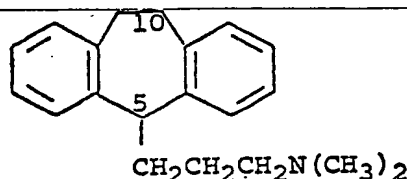
The board also affirmed the examiner's rejection of all claims as obvious over Villani.² In treating this rejection we again select claim 3 as illustrative, since it is drawn to the one compound, of all those covered by the appealed claims, which is closest to the prior art, i.e., to Villani.

It will be recalled that the structural formula of the principal compound claimed in claim 3 is

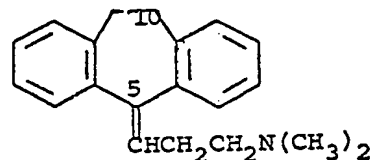


²Villani et al., "Dialkylaminoalkyl Derivatives of 10, 11-Dihydro-5H-dibenzo [a,d] cycloheptene and Related Compounds," *Journal of Med. & Pharm. Chem.*, vol. 5, pp. 373-83 (1962).

Villani discloses two series of 5-aliphatic substituted derivatives of dibenzo [a,d] cycloheptadiene, one series being saturated and the other unsaturated. As a specific member of the saturated series, Villani discloses an isomer of the above compound of claim 3. The structure of the isomer is



As a specific member of the unsaturated series, Villani discloses a compound, known commercially as amitriptyline, having the following structure:



It will be noted that in the isomer the dimethylamino group is attached to the cycloheptadiene ring through a CH_2 group, by a single bond, and hence is saturated in the same sense that the claimed compound is saturated; in amitriptyline the dimethylamino group is attached to the ring through a CH group, by a double bond, and hence is unsaturated in that sense. Villani discloses that each series of compounds has medicinal properties related to the central nervous system.

It was the view of the examiner that the disclosure by Villani of the 5-substituted isomer of the claimed 10-substituted compound rendered the claimed compound obvious, "since appellant has failed to establish that the claimed isomeric compound possesses any unexpected properties over" the 5-position isomer of Villani.

Appellant sought to establish unobviousness via the unexpectedly-superior-property route. He cited the Protiva reference,³ which, like Villani, discloses both a saturated series including the isomer of the claimed compound and an unsaturated series including amitriptyline.

³Protiva et al., "A New Group of Tranquillizers: Derivatives of 2,3:6,7-Dibenzosuberane and 2,3:6,7-Dibenzo-4-suberene," *Journal of Med. & Pharm. Chem.*, vol. 4, pp. 411-15 (1961).

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Protiva indicates that certain of the unsaturated compounds are better tranquilizers than the saturated ones. Protiva also states that "Aminoalkyl derivatives with a saturated side chain *** are less interesting in regard to tranquillizing activity."

Appellant introduced an affidavit of a chemist indicating that a comparative test of the claimed compound and amitriptyline revealed that the claimed compound was about 1.7 times as active as amitriptyline in terms of group.

Appellant introduced an affidavit of a chemist indicating that a comparative test of the claimed compound and amitriptyline revealed that the claimed compound was about 1.7 times as active as amitriptyline in terms of certain effects on the central nervous system of rats. Appellant presented no evidence directly comparing the claimed compound and the isomer.

Appellant's position involves a kind of indirect showing of unexpected superiority. He contended that the statements in Protiva and Villani indicate that the unsaturated derivatives are more active than the saturated ones, and his evidence showed that the claimed compound was more active than the best of the unsaturated derivatives; ergo, it is unexpectedly better than the saturated derivatives, such as the 5-position isomer, disclosed in Villani.

The examiner and the board found appellant's evidence and argument unpersuasive. The board held that "The comparative affidavit *** does not demonstrate that a claimed product exhibits any property different from that exhibited by the structurally most closely related reference compound, the isomeric compound." While it did not say that a direct comparative showing was necessarily required, the board held that the evidence adduced was not "clear and convincing," because the statements of Villani and Protiva are general in nature, pertaining to activity on the central nervous system, and are not comparable to the specific property tested and reported in the affidavit, i.e., antidepressant activity in rats. The board noted that the affidavit did not set forth any comparative information on toxicity, apparently suggesting that the statements of "superiority" in Villani and Protiva could have pertained to low toxicity as well as to high activity.

It is our conclusion that appellant's evidence was sufficient to establish unobviousness of the claimed compound. We think the teachings of Protiva and Villani, while broad, were of such a nature as to lead away from the saturated 10-position isomer of claim 3 as a tranquilizer. We note especially the

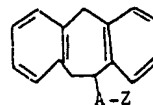
above-quoted statement of Protiva that "Aminoalkyl derivatives with a saturated side chain *** are less interesting in regard to tranquillizing activity." This, coupled with the facts that in the claimed compound the dimethylaminopropyl radical is substituted on the opposite side of the cycloheptadiene ring from the 5 position and has better antidepressant activity in laboratory animals than the best unsaturated prior art compound, lead us to conclude that the compound was unobvious.

Sufficiency of Disclosure—Markush Group

The board also affirmed the examiner's rejection of claim 1 on the ground of insufficient disclosure, 35 U.S.C. 112, first paragraph. The solicitor indicates, as the examiner and the board unfortunately did not, that the insufficiency is with regard to the how-to-make and how-to-use provisions of that paragraph. We find that the issue of compliance with the how-to-use provision was fairly raised by the examiner's remarks in the final rejection and the examiner's answer. Since we agree with the Patent Office on the how-to-use question, we shall not consider any possible how-to-make issue.

Claim 1 reads:

1. A dibenzo [a,d] a cycloheptadiene derivative of the formula:



and its acid addition salts and quaternary ammonium derivatives in which A is a divalent, saturated, aliphatic hydrocarbon chain of 2 to 5 carbon atoms, such that at least 2 carbon atoms separate the radical Z from the dibenzo-cycloheptadiene ring, and Z is a member selected from the group consisting of amino, monoalkylamino, dialkylamino, in which the alkyl radicals contain 1 to 5 carbon atoms each, and 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, and 4-alkyl-1-piperazinyl in which the alkyl radical contains 1 to 5 carbon atoms, and such rings substituted by at least one alkyl radical of 1 to 5 carbon atoms each.

The examiner's view was that the specification was inadequate to enable one skilled in the art to use the broad invention defined by claim 1, although he apparently agreed that it was adequate to enable the use of some species within the claim. We observe that the Patent Office proceedings in this case oc-

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curred before our decisions last term on "undue breadth" e.g., *In re Borkowski*, 57 CCPA 946, 422 F.2d 904, 164 USPQ 642 (1970), yet the examiner saw the problem as one of lack of support under the first paragraph of § 112. The examiner noted that the definition of Z in the claim was by a Markush group including both aliphatic and heterocyclic members. His position was that the specification did not enable the use of those compounds within the claim having heterocyclic moieties.

[3] Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in *In re Robins*, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use *some* technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art.

It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group. The examiner and the board did not believe that appellant had done so as to the heterocyclic members of the group. While they noted the absence of examples using heterocyclic moieties, we do not find that they viewed examples as mandatory. The issue before us is whether appellant has provided *any* teaching of how to use compounds containing the heterocyclic members of the Markush group.

The only reference to heterocyclic radicals in the specification is the statement that "the invention provides" compounds of the structure shown in claim 1, wherein Z may be, among other possibilities,

a mononuclear, nitrogen-containing heterocycle connected to the chain A by the nitrogen atom, and optionally containing an oxygen, sulphur, or second nitrogen atom in the ring and optionally substituted by one or more alkyl radicals containing 1 to 5 carbon atoms each, such as 1-pyrrolidyl, piperidino, morpholino, 1-piperazinyl, or 4-alkyl-1-piperazinyl.

There later appear statements that the compositions of the invention may be used

"for therapeutic purposes" and may be administered orally, rectally or parenterally.

[4] It appears that the examiner and the board doubted that compositions having heterocyclic moieties would be useful at all for therapeutic purposes. While this position could have led to a rejection under § 101, it also leads to a rejection under the how-to-use provision of § 112, since if such compositions are in fact useless, appellant's specification cannot have taught how to use them.

[5] We find that these doubts of the Patent Office were reasonable under the circumstances. We particularly note the following passage from the board's opinion:

The products herein are alleged to exhibit several different properties. It is not to be expected that the heterocyclic compounds claimed will necessarily exhibit the same properties as those of the exemplified open chain amines. With respect to the rejection on Villani et al., appellant relies upon the Ducrot affidavit in this record to demonstrate significant differences in properties varying with structural variations. Protiva et al., cited by appellant, demonstrates that heterocyclic substituents cause variations in properties of the same order of magnitude as those in said affidavit.

Accordingly, the burden was on appellant to show that his teaching of using such compositions for therapeutic purposes was true. See *In re Cook*, 169 USPQ 298; *In re Marzocchi*, 169 USPQ 367.

[6] Appellant, in seeking to carry this burden, urges that all the claimed compositions have *some* therapeutic utility, even if not to the same degree as the preferred compositions. If this is so, appellant will have overcome the how-to-use rejection, since we know of no requirement in § 112 that all the compositions within a claim have to have the same degree of utility, although the board's language may have suggested the contrary. Appellant's urging on this point is not supported by the record. We find no evidence overcoming the reasonable doubts of the Patent Office that compositions within the claim having heterocyclic moieties can be used for therapeutic purposes. Accordingly, the board's decision affirming the rejection of claim 1 is affirmed.

Summary

The decision of the board is *affirmed* as to claim 1 and *reversed* as to claims 2 and 3.

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App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean plant, however there was no basis for judging the practical significance of data with regard to maturity date, flowering date, flower color, or height of the plant.). See also *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and *In re Eli Lilly*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP § 716.02(c).

APPLICANTS HAVE BURDEN OF EXPLAINING PROFFERED DATA

"[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992).

DIRECT AND INDIRECT COMPARATIVE TESTS ARE PROBATIVE OF NONOBVIOUSNESS

Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See *In re Blondel*, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and *In re Fouche*, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a *prima facie* case of obviousness.

The patentability of an intermediate may be established by unexpected properties of an end product "when one of ordinary skill in the art would reasonably ascribe to a claimed intermediate the 'contributing cause' for such an unexpectedly superior activity or property." *In re Magerlein*, 602 F.2d 366, 373, 202 USPQ 473, 479 (CCPA 1979). "In order to establish that the claimed intermediate is a 'contributing cause' of the unexpectedly superior activity or property of an end product, an applicant must identify the cause of the unexpectedly superior activity or property (compared to the prior art) in the end product and establish a nexus for that cause between the intermediate and the end product." *Id.* at 479.

716.02(c) Weighing Evidence of Expected and Unexpected Results

EVIDENCE OF UNEXPECTED AND EXPECTED PROPERTIES MUST BE WEIGHED

Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (Claims directed to a method of effecting

analgesia without producing physical dependence by administering the levo isomer of a compound having a certain chemical structure were rejected as obvious over the prior art. Evidence that the compound was unexpectedly nonaddictive was sufficient to overcome the obviousness rejection. Although the compound also had the expected result of potent analgesia, there was evidence of record showing that the goal of research in this area was to produce an analgesic compound which was nonaddictive, enhancing the evidentiary value of the showing of nonaddictiveness as an indicia of nonobviousness.). See MPEP § 716.01(d) for guidance on weighing evidence submitted to traverse a rejection.

Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) (Claims were directed to a display/memory device which was *prima facie* obvious over the prior art. The court found that a higher memory margin and lower operating voltage would have been expected properties of the claimed device, and that a higher memory margin appears to be the most significant improvement for a memory device. Although applicant presented evidence of unexpected properties with regard to lower peak discharge current and higher luminous efficiency, these properties were not shown to have a significance equal to or greater than that of the expected higher memory margin and lower operating voltage. The court held the evidence of nonobviousness was not sufficient to rebut the evidence of obviousness.); *In re Eli Lilly*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (Evidence of improved feed efficiency in steers was not sufficient to rebut *prima facie* case of obviousness based on prior art which specifically taught the use of compound X537A to enhance weight gain in animals because the evidence did not show that a significant aspect of the claimed invention would have been unexpected.).

EXPECTED BENEFICIAL RESULTS ARE EVIDENCE OF OBVIOUSNESS

"Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) (resultant decrease of dental enamel solubility accomplished by adding an acidic buffering agent to a fluoride containing dentifrice was expected based on the teaching of the prior art); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims at issue were directed to a process of sterilizing a polyolefinic composition which contains an antioxidant with high-energy radiation. Although evidence was